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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

1059 7590 08/22/2002

BERESKIN AND PARR
SCOTIA PLAZA
40 KING STREET WEST-SUITE 4000 BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/22/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/402,488	MOLONEY ET AL.	
	Examin r	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *31-40 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-47 are pending in the application.

Applicants' amendment to claims 1, 4, 7, 9-11, 13, 14, 17, and 27 in Paper No. 19, filed 06/04/02 is acknowledged.

Claims 1-30 and 41-44 are being examined on the merits.

Claims 31-40 and 45-47 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 14.

Applicants' arguments filed in Paper No. 19 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

1. Rejection of claims 1-30 and 41-44 under 35 U.S.C. 112, second paragraph, as being indefinite is maintained. Claims 1 (claims 4-19 dependent therefrom), 2-4, 21-23, 41 (claims 43 and 44 dependent therefrom), and 42 as being indefinite in the recitation of "derived from" is maintained. The rejection was fully explained in a previous Office action. Applicants argue the term is meant to include a pro-peptide that is part of or isolated from an autocatalytically maturing zymogen as well as any mutant forms or variants of a pro-peptide derived from an autocatalytically maturing zymogen. Applicants' argument is not found persuasive. MPEP 2173.02 states "[I]f the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate". It is unclear from the claims as to the derivatives of a pro-peptide from an autocatalytically maturing zymogen to which applicants refer and

therefore, one of skill in the art would not recognize the scope of pro-peptides "derived from" an autocatalytically maturing zymogen. The rejection is maintained for the reasons discussed above and the reasons of record.

Claim Rejections - 35 USC § 112, First Paragraph

2. The scope of enablement rejection of claims 1-26, 28-30, and 41-44 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action. Applicants argue claim 1 has been amended to specify that a mature form of an autocatalytically maturing zymogen is added to the fusion protein in step c) and that the amendment further clarifies the conditions required to result in cleavage of the pro-peptide and release of the recombinant polypeptide. Applicants argue that further limitation of the claims is not necessary and the combination of pro-peptides, cleaving proteases, and conditions for cleavage could readily be determined by a skilled artisan. Applicants' argument is not found persuasive.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). As written, the claims are so broad as to encompass a method of preparing a recombinant polypeptide by: a) transforming a host cell with an expression vector comprising: (1) a promoter sequence, (2) a chimeric nucleic acid sequence comprising a nucleic acid encoding *any* pro-peptide derived from *any* autocatalytically maturing zymogen, protease, aspartic, serine or cysteine protease, upstream of a nucleic acid encoding a heterologous polypeptide, (3) a termination sequence; b) growing the host cell to produce the fusion protein; and c) adding *any* mature form of an autocatalytically maturing zymogen to the fusion protein resulting in cleavage of the fusion protein from the recombinant polypeptide and optionally altering the pH, salt, or temperature conditions. Applicants have provided *only*

two working examples of the claimed chimeric nucleic acid sequence, i.e., an expression vector encoding a GST—chymosin pro-peptide—hirudin polypeptide cleavable by treatment with chymosin at pH 4.5 (pages 14 and 15) or a His tag—chymosin pro-peptide—carp growth hormone polypeptide cleavable by treatment with chymosin at pH 2 (page 17, top) or red turnip beetle gut extract (page 17 bottom). Neither the specification nor the prior art provides sufficient guidance as to which combination of proteases and pro-peptides that would result in cleavage of a fusion protein from a recombinant protein or the altered conditions of pH, salt, or temperature under which cleavage using a particular combination is likely to occur. It is not routine in the art to screen for a pro-peptide for cleavage by any protease and optionally under any altered conditions which cleavage can occur as encompassed by the claims. While applicants have provided two examples of heterologous proteases that cleave the chymosin pro-peptide, i.e., Sigma 2143 and Aspergillus saitoi acid protease (see Paper No. 17), the claims are not so limited to a chimeric nucleic acid comprising a nucleic acid encoding only a chymosin pro-peptide and furthermore, it is unpredictable as to whether these proteases (Sigma 2143 and Aspergillus saitoi acid protease) will cleave *any* pro-peptide of an autocatalytically maturing zymogen. Neither the specification nor the prior art provide sufficient guidance as to which combination of proteases and cleavable heterologous pro-peptides and optionally altered conditions as encompassed by the claims that would obtain the desired biological effect. The expectation of making and using the claimed polynucleotide, host cell, or composition of claims 20-26, 28-30, and 41-44 or practicing the method of claims 1-19 is highly unpredictable and would require an undue amount of experimentation. Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In regards to claim 41, as stated in a previous Office action, the term "pharmaceutical" implies a treatment of a disease. It is unpredictable what diseases can be effectively treated using a "pharmaceutical composition" comprising the claimed chimeric nucleic acid. Neither the specification nor the prior art provide sufficient guidance as to what specific diseases could be treated by administering a

"pharmaceutical composition" comprising said chimeric nucleic acid. Applicants have provided no working examples of diseases that can be treated by the claimed "pharmaceutical composition". Therefore, one of skill in the art would be left to identify a disease treatable using such a "pharmaceutical composition", thus constituting undue experimentation.

Claim Rejections - 35 USC § 102/103

3. Claims 1-7, 9-13, 15-26, 28-30, and 41-44 are rejected under 35 U.S.C. 102(a) as being anticipated by, or in the alternative as being unpatentable over Moloney (WO 96/21029). The rejection was fully explained in a previous Office action.

Moloney teaches a method for expression and release of a recombinant polypeptide in a host cell by: a) introducing into a host cell a chimeric DNA sequence comprising: 1) a first DNA sequence capable of regulating transcription in said host, 2) a second DNA sequence encoding a recombinant fusion polypeptide comprising a DNA sequence encoding a recombinant polypeptide and a DNA linker sequence encoding an amino acid sequence that is specifically cleavable by enzymatic or chemical means located between the sequences encoding an oleosin gene and a recombinant polypeptide and 3) a third DNA sequence encoding a termination region functional in the host; b) growing the host to produce the recombinant fusion polypeptide; and c) contacting the fusion protein with said enzymatic or chemical means such that the recombinant polypeptide is released from the fusion polypeptide (page 3, lines 14-26) and also teach that the peptide linker preferably includes a protease target motif (page 20, line 1). Moloney teaches that a protease specific for the protease recognition motif can be added for release of the recombinant polypeptide (page 28, bottom). Moloney teaches an example of such a fusion protein may be a chymosin precursor/oleosin fusion protein and teaches that a chymosin recognition site be included between the oleosin and the chymosin protein sequences (page 29). Moloney also teaches the fusion protein "may be capable of undergoing self-release" and provide an example as follows: "the proteolytic enzyme chymosin undergoes self-activation from a precursor to an active protease by exposure of the precursor to low pH conditions. Expression of the chymosin precursor/oleosin fusion

protein to conditions of low pH will activate the chymosin. If a chymosin recognition site is included between the oleosin and the chymosin protein sequences, the activated chymosin can then cleave the fusion proteins. This is an example of self release that can be controlled by manipulation of the conditions required for enzyme activity" (p 29, lines 3-10). Moloney also teaches "for uses where the fusion protein contains a peptide hormone that is released upon ingestion, the protease recognition motifs may be chosen to reflect the specificity of gut proteases to simplify the release of the peptide" (page 20, lines 7-10). Moloney teaches that the recombinant polypeptide to be produced as a fusion may include growth hormones (page 24, lines 19 and 20), the anticoagulant hirudin (page 25, lines 4 and 5), additives for animal feeds (page 24, line 17), for use in the food industry (page 24, line 27), proteins with a therapeutic or diagnostic value (page 25, lines 1-2).

Applicants assert the examiner suggests that Moloney teaches the preparation of a fusion protein as follows: NH_3-Chymosin---Pro-Chymosin---Oil Body Protein-COO^-. Applicants argue this would require preparation of a construct wherein the pro-sequence is separated from and appears downstream from the mature chymosin. Applicants argue there is no motivation to prepare such a sequence and it would be questionable as to whether or not cleavage resulting in a mature chymosin would occur. Applicants' argument is not found persuasive. Regarding applicants' argument as to the motivation and expectation of success to prepare such a polynucleotide or method of use thereof for producing a recombinant protein, Moloney anticipates claims 1-7, 9, 13, 15, 19-26, 28-30, and 41-44 and therefore, no motivation or reasonable expectation of success for practicing the claimed invention is required for claims rejected under 35 USC 102(b). Claims 10-12 and 16-18 are rendered obvious by Moloney. For example, Moloney teaches "for uses where the fusion protein contains a peptide hormone that is released upon ingestion, the protease recognition motifs may be chosen to reflect the specificity of gut proteases to simplify the release of the peptide" (page 20, lines 7-10). One of ordinary skill in the art would have recognized that chymosin is a gut protease, and therefore, based on the teachings of Moloney, would have designed a nucleic acid for production of a fusion protein with a chymosin recognition sequence for release of the recombinant protein. Therefore, Moloney provides sufficient motivation and a reasonable expectation of

success to practice the method of claims 10-13 and 16-18 Therefore, claims 1-7, 9-13, 15-26, 28-30, and 41-44 are anticipated by, or at least rendered obvious, by Moloney.

Claim Rejections - 35 USC § 103

4. Rejection of claim 8 is under 35 U.S.C. 103(a) as being unpatentable over Moloney (WO 96/21029) in view of McCaman et al. (J Biol Chem 261:15345-15348) is maintained. The rejection was fully explained in a previous Office action. Applicants argue the deficiencies in Moloney are not remedied by McCaman and further argue that McCaman does not teach or suggest the claimed invention. Applicants' argument is not found persuasive. As stated above, Moloney anticipates claim 7 from which claim 8 depends. The teachings of Moloney in combination with the teaching of McCaman that chymosin is activated at pH 2 and is processed to a mature form at pH 4.5 would render obvious claim 8 for the reasons discussed in a previous Office action. The rejection is maintained for the reasons discussed above and for the reasons of record (see Paper Nos. 15 and 18).

5. Rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over Moloney (WO 96/21029) in view of Fine et al. (Gen Comp Endocrinol 89:51-61) is maintained. The rejection was fully explained in a previous Office action. Applicants argue the deficiencies in Moloney are not remedied by Fine and further argue that Fine does not teach or suggest the claimed invention. Applicants' argument is not found persuasive. As stated above, Moloney anticipates claim 26 from which claim 27 depends. The teachings of Moloney in combination with the teaching of Fine who discloses the nucleotide sequence of carp growth hormone (cGH), expression of cGH in E. coli, and that administration of purified cGH to carp fed a low protein diet increased growth by 38 % relative to vehicle would render obvious claim 27 for the reasons discussed in a previous Office action. The rejection is maintained for the reasons discussed above and for the reasons of record (see Paper No. 18).

Conclusion

6. No claim is in condition for allowance. All claims are rejected.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600